DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

94239d

CBER-00- 007

NOV 29 1999

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Robert Floc'h
Vice President and General Manager
IMTIX – SangStat
Etablissement de Marcy
1541 Avenue Marcel Merieux
F – 69280 Marcy L'Etoile, France

Dear Mr. Floc'h:

The Food and Drug Administration (FDA) conducted an inspection of IMTIX – SangStat, located at Etablissement de Marcy, 1541 Avenue Marcel Merieux, F – 69280 Marcy L'Etoile, France, between July 19, 1999, and August 6, 1999. During the inspection, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680, Title 21, Code of Federal Regulations (21 CFR). The deviations noted on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection include, but are not limited to the following:

1. Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.113(b) and 211.110]. For example, in-process material was tested for the presence of microorganisms with no established alert and action limits. Furthermore, microbial test results for these in-process samples taken during the manufacturing of Thymoglobulin fell in the range of 83 – 7200 colony forming units (cfu)/ml and no investigations were performed.

2. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192]. For example, no investigations were performed to determine the source of increasing bioburden levels found in samples of product taken after [redacted]

3. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67]. For example, the effectiveness of the cleaning and sanitization process to ensure the removal of microorganisms had not been established.

4. Failure to exercise appropriate controls over and to routinely calibrate, inspect, or check for accuracy automatic, mechanical, or electronic equipment used in the manufacture, processing, packaging, and holding of a drug product according to a written program designed to assure performance [21 CFR 211.68], in that the pressure gauges used to conduct post use integrity testing of filters used during manufacturing were never calibrated.

5. Failure to assure that each person engaged in the manufacture, processing, packing, or holding of a drug product has training and experience to enable that person to perform the assigned functions [21 CFR 211.25], in that there was no documentation that employees who perform water sampling had received initial training in sample collection and subsequent training in response to implicated sampling errors.

6. Failure to establish appropriate time limits for the completion of each phase of production to assure the quality of the drug product [21 CFR 211.111]. For example, the concentration/diafiltration processing step for intermediates had no established or validated time limits for completion of the process.

7. Failure of the licensed manufacturer to promptly notify the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), of errors and accidents in the manufacture of products that may affect the safety, purity, or potency of any product [21 CFR 600.14], in that the temperature excursion for [redacted] vials of Thymoglobulin lot TH005 was not reported to CBER. The vials were exposed to temperatures of 19°C to 24°C for approximately 2 days.

We acknowledge receipt of your written responses dated September 15, 1999, and October 15, 1999, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. We have reviewed the contents of your response. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. In addition, your response to this letter should include time frames for completion of all corrective

actions. Our comments and requests for further information regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Item 1A

We acknowledge your commitment to not release any reprocessed Thymoglobulin product for distribution in the United States until the issues with [redacted] have been resolved. Your response states the [redacted] that you are using has a Drug Master File (DMF) reference number DMF[redacted]. In order for a review to be conducted, please provide a letter of authorization from the manufacturer of the [redacted] to your firm which authorizes reference to the DMF. The letter of authorization should specify to whom the authorization is granted, the component or material being described, and where the information and data is located in the file by page number and date of submission. In addition, please indicate what procedures are in place to prevent the use of chemical raw materials which have not been tested or have not met U.S. Pharmacopeial (USP) methods and standards.

Item 1B

We have reviewed your Protocol EL0003/01 and Report ER0020/01 entitled "Chromatography Columns Storage Solution Bioburden Study Thymoglobulin" and have the following comments:

- Section 4.1 of both the Protocol and Report state that "A level of [redacted] times the number that corresponds to [redacted] of the population is used for determining the bioburden action level." We believe the calculation method provides an unacceptable action limit. Please provide the scientific rationale and the data to support your calculation method for determining the action limit. In addition, please indicate what procedures are in place for establishing an alert limit.

- Section 7.2 of the Report states that *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli* are microorganisms identified as human pathogens. We reviewed the data you provided and found there is evidence of human pathogenic fecal bacteria such as, *Enterobacter cloacae, Enterobacter agglomerans, Serratia liquifaciens, Enterococcus Group D, and Escherichia hermanii,* as well as other objectionable organisms such as, *Streptococcus sanguis, Streptococcus mitis,* and *Brevidomonas cepacia.* Please be advised that these organisms should be added to the list of microorganisms identified as human pathogens. Furthermore, the presence of any microorganisms identified as a human pathogen, regardless of the action or alert limit, should result in a thorough and complete investigation.

Item 1C

We have reviewed your Protocol EL0004/01 and Report ER0021/01 entitled "Final Bulk Storage Period Determination Thymoglobulin" and have the following comments:

- The parameters for testing specified in Section 6 of the Protocol and Section 5 of the Report have not been identified as stability indicating. The parameters tested should

include an assay indicative of product stability, e.g. potency assay. Furthermore, your response states that "The other characteristics of the product are routinely tested for release of the corresponding finished product." This is not an acceptable practice. Please be advised that the ability of a final product to meet release testing specifications can not be used to validate the storage period with respect to product stability.

- Section 8 of the Report states that the study supports the "Thymoglobulin Final Bulk Product storage period up to [redacted] weeks at [redacted], before filling," however, the data do not support this conclusion. Passing test results for stability indicating parameters on at least 3 lots of bulk product held for 6 weeks are needed in order to assign a validated storage period of [redacted] weeks.

Items 1D and 2A-1

We have reviewed your Protocol EL0002/01 and Report ER0019/01 entitled, "Thymoglobulin In-Process Bioburden Study" and have the following comments:

- Section 4.1 of both the Protocol and Report state that "A level of [redacted] times the mean is used as the bioburden alert level." We believe the calculation method provides an unacceptable alert limit. Please provide the scientific rationale and the data to support your calculation method for determining the alert level.

- Section 4.2 of both the Protocol and Report state that "A level of [redacted] times the mean is used as the bioburden action level." We believe the calculation method provides an unacceptable action limit. Please provide the scientific rationale and the data to support your calculation method for determining the action limit.

- Section 7.2 and 8.1 of the Report states that *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli* are microorganisms identified as human pathogens. We reviewed the data you provided and found there is evidence of human pathogenic fecal bacteria such as, *Enterobacter cloacae, Enterobacter agglomerans, Serratia liquifaciens, Enterococcus Group D, and Escherichia hermanii,* as well as other objectionable organisms such as, *Streptococcus sanguis, Streptococcus mitis,* and *Brevidomonas cepacia.* Please be advised that these organisms should be added to the list of microorganisms identified as human pathogens. Furthermore, the presence of any microorganisms identified as a human pathogen, regardless of the action or alert limit, should result in a thorough and complete investigation.

Please be advised the observations 1A, 1C, and 1D noted commitments your firm had previously made and included in a letter to the FDA dated March 23, 1999, that had not been completed. Please ensure that the commitments for observations 1A, 1C, and 1D are completed and the required information for observations 1A, 1B, 1C, 1D, and 1E are submitted to the license application.

Item 2A-2

We have reviewed your Protocol EL0005/01 and Report ER0022/01 entitled "Determination of the Storage Period of [redacted] Treated Red Blood Cells Thymoglobulin" and have the following comments:

- Section 4.1 of both the Protocol and Report state that "A level of [redacted] times the number that corresponds to [redacted] of the population is used for determining the bioburden action level." We believe the calculation method provides an unacceptable action limit. Please provide the scientific rationale and the data to support your calculation method for determining the action limit. In addition, please indicate what procedures are in place for establishing an alert limit.

- Section 8.1 of the Report states that "The storage period up to 6 days is validated. As there is no difference in the bioburden levels before and after storage, the monitoring of [redacted] RBC will be performed on samples taken before storage. An interim action level of bioburden was determined as [redacted] before and after storage." However, the study and supporting data do not support this conclusion. The data analysis actually demonstrates that 1) there is an increase in the number of contaminant counts over 20 CFU/ml after storage for 5 and 6 days; 2) there is a difference in the bioburden levels before and after storage; and 3) the storage period up to 6 days is not validated.

Item 2B, 2C, and 2D

Although your response states that "However, bioburden tests taken from subsequent processing steps demonstrate the ability of the process to reduce/remove the organisms seen," you have provided no data which demonstrate the adequate removal of pyrogens from product with extremely high levels of bioburden. Please be advised, that the practice of using components or starting materials known to be contaminated with microorganism(s) and then testing at a subsequent step for the presence of the microorganism(s) is unacceptable. Please describe what procedures are in place to assure that in-process bioburden test results failing to meet specifications will be thoroughly investigated.

Item 2E

We acknowledge your commitment to a study to demonstrate removal of microorganisms on 3 consecutive batches. Please provide a timeframe for which completion of the study is expected. Additionally, please provide a summary of the data when complete.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all inclusive list of the deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with all requirements of the federal regulations. You should take prompt action to correct these deviations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, license suspension, or revocation.

Your reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448.

Sincerely,

Deborah D. Ralston
Director
Office of Regional Operations

cc: Jean Jacques Bienaime
CEO/President
SangStat Medical Corporation
Freemont, CA 94555